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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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			1642	

DATE MAILED: 05/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/619,310	THASTRUP ET AL.
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 03 March 2005.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-41 is/are pending in the application.
- 4a) Of the above claim(s) 10-22,26-31 and 33-39 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-9, 23-25,32,40 and 41 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 19 July 2000 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) - - - - - | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>20030306; 20040519</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

1. The election with traverse filed March 2, 2005 is acknowledged and has been entered.

Applicant has elected the invention of Group III, claims 7 and 40, drawn to a fluorescent protein having the amino acid sequence depicted in Figure 5 (SEQ ID NO: 22).

2. Claims 1-41 are pending in the application. Claims 10-22, 26-31, and 33-39 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed March 2, 2005.

3. Claims 1-9, 23-25, 32, 40, and 41 are currently under prosecution.

Election/Restrictions

4. Applicant's traversal of the restriction and election requirement set forth in the Office action mailed November 2, 2004 is acknowledged.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

Applicant has submitted that the linking claims have not been properly considered and that the present claims relate to various mutations in GFP, all of which result in an increase in fluorescence intensity. Furthermore, Applicant has asserted, although admitting that the claims encompass variants of GFP having different chromophores and different amino acids adjacent to these chromophores, each of the variants is not functionally unrelated.

In reply, it is recognized that claim 1, for example, is a linking claim; and contrary to Applicant's submission, all linking claims have been identified and treated in

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accordance with current practice, as set forth in section 6 of the previous Office action mailed November 2, 2004.

Contrary to Applicant's submission, the claims are not limited to variants of GFP; rather, the claims are more broadly drawn to fluorescent proteins that are derived from GFP or any functional analogue thereof. Although each fluorescent protein that is encompassed by the claims has increased fluorescence intensity relative to the fluorescence protein from which it is derived, as Applicant has remarked, the claims encompass fluorescent proteins having different chromophores and different amino acids adjacent to these chromophores. Because the ability of the protein to fluoresce is attributable to the presence of the structural feature that is the chromophore and because each chromophore differs, there is no correlation between a common particularly identifying structural feature and their common functional property to fluoresce.

MPEP § 803 states there are two criteria for a proper requirement for restriction between patentably distinct inventions: (a) the inventions must be independent or distinct as claimed; and (b) if restriction is required, there must be a serious burden on the Examiner.

The inventions of Groups I-XI are patentably distinct, each from the other, for the reasons set forth in section 7 of the previous Office action. As also explained in section 7 of the previous Office action, because the inventions are patentably distinct, the search required to examine any one of the different inventions is not the same, nor is it coextensive with the search required to examine any other. Therefore, a different search would have to be performed to examine claims drawn to each different invention; and consequently, searching and examining claims drawn to more than one invention would be unduly burdensome.

Accordingly, the restriction and election requirement is proper and therefore made FINAL.

Priority

5. Applicant's claim under 35 USC § 120 for benefit of the earlier filing date of the 08/819,612, filed March 17, 1997, which claims benefit of PCT Application No. PCT/DK96/000511, filed January 31, 1996, which claims benefit of Denmark Patent Application No. 1065/95, filed January 31, 1996, is acknowledged.

However, claims 23-25 and 32 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely July 19, 2000.

Information Disclosure Statement

6. The information disclosures filed March 6, 2003 and May 19, 2004 have been considered. An initialed copy of each is enclosed.

Specification

7. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

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An example of such an improperly demarcated trademark includes GenBank™ (page 7, line 22, and elsewhere) and Axiovert™ (page 19, line 3).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

8. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Claim 9 recites, "the polypeptide is a kinase, preferably the catalytic subunit of protein kinase A, or protein kinase C, or Erk1, or a cytoskeletal element". However, the specification fails to provide proper antecedent basis for the claimed subject matter.

9. The specification is objected to because at page 19, line 14, it refers to "Table 1"; however, "Table 1" cannot be found in the specification or the file and appears to have been omitted. Appropriate correction is required.

Claim Objections

10. Claims 1-9, 23-25, 32, and 41 are objected to because the claims are drawn to the subject matter of nonelected inventions.

11. Claim 3 is objected to because the claim recites, "[a] fluorescent protein according to claim 1 resulting in an increased fluorescence". The claim is directed to a product, as opposed to a process comprising an active step that achieves such a result. Moreover, a protein does not "result" in an increased fluorescence. A protein may have

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or exhibit increased fluorescence, or the mutation in the protein upon its derivation may cause increased fluorescence. Appropriate correction is required.

12. Claims 8 and 9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 8 recites, "consisting of a fluorescent protein (GFP) accordingly to claim 1", but also recites, "wherein said GFP is linked to a polypeptide". A fluorescent protein according to claim 1 is a fluorescent protein; it is not a fluorescent protein linked to a polypeptide. Consequently, claims 8 and 9 broaden, rather than narrow, the scope of claim 1.

13. Claim 4 is objected to because "Aequora victoria" is misspelled as "Aequora victorea". Appropriate correction is required.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claim 5, 6, 8, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is indefinite because the claim recites, "wherein the amino acid F in position 64 of GFP or Y66H-GFP has been substituted". Claim 1 depends from claim 1, which lacks an antecedent basis to support the recitation, since claim 1 does not describe an amino acid sequence having per se the amino acid F in position 64 of GFP. Moreover, claim 1 does not provide antecedent basis for Y66H-GFP, or an amino acid sequence having per se the amino acid F in position 64 of Y66H-GFP. Accordingly, the

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metes and bounds of the subject matter that Applicant regards as the invention cannot be determined.

Claim 6 is indefinite because the claim recites, "wherein the amino acid F in position 1 preceding the chromophore has been substituted". Claim 1 depends from claim 1, which lacks an antecedent basis to support the recitation, since claim 1 does not describe an amino acid sequence having per se the amino acid F in position 1 preceding the chromophore. Accordingly, the metes and bounds of the subject matter that Applicant regards as the invention cannot be determined.

Claim 8 is indefinite because the claim recites, "consisting of a fluorescent protein (GFP) accordingly to claim 1", but also recites, "wherein said GFP is linked to a polypeptide". A fluorescent protein according to claim 1 is a fluorescent protein; it is not a fluorescent protein linked to a polypeptide. Therefore, a fusion protein consisting of a fluorescent protein accordingly to claim 1 cannot comprise a linked polypeptide. Accordingly, the metes and bounds of the subject matter that Applicant regards as the invention cannot be determined.

Claim 41 is indefinite because the claim recites, "wherein the amino acid F in position 1 preceding the chromophore has been substituted". Claim 1 depends from claim 1, which lacks an antecedent basis to support the recitation, since claim 1 does not describe an amino acid sequence having per se the amino acid F in position 1 preceding the chromophore. Accordingly, the metes and bounds of the subject matter that Applicant regards as the invention cannot be determined.

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 23-25 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

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one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

Claims 23-25 and 32 are directed to a genus of fluorescent proteins that are derived from "wild-type Green Fluorescent Protein (GFP) comprising a chromophore having three amino acid residues selected from the group consisting of SYG, SHG, TYG and THG".

The specification describes the amino acid sequence of "a preferred sequence of the gene encoding GFP derived from *A. victoria*" (page 7, lines 13 and 14; Figure 2; SEQ ID NO: 15), which putatively encodes the predicted amino acid sequence of "a wild-type Green Flourescent Protein (GFP)" (i.e., SEQ ID NO: 16). As further disclosed at page 3, lines 10-12, this "wild-type GFP" comprises the chromophore SYG at positions 65-67 in the predicted primary amino acid sequence. However, it does not appear that the specification provides written support for a "wild-type GFP" comprising chromophores of SHG, TYG, or THG. In fact, the specification discloses that the blue fluorescing variant designated Y66H-GFP, which comprises the chromophore SHG, is not a "wild-type GFP" (i.e., natural GFP) but a recombinant fluorescent protein produced by random *in vitro* mutagenesis of a complementary DNA (cDNA) molecule encoding the naturally occurring protein (page 1, lines 19-28).

Claim 24 is directed to a fluorescent protein according to claim 23, which further comprises an amino acid substitution involving one or more of the three amino acid residues of the chromophores SYG, SHG, TYG or THG. The specification provides written support for substituting tyrosine in the middle position of the chromophore SYG with histidine (e.g., page 1, lines 19-28). The specification provides written support for substituting serine in the first position of the chromophore SYG with threonine (e.g., page 2, lines 10-13). In addition, the specification provides support for substitutions at the phenylalanine at the position preceding the first position of the chromophores SYG, SHG, and TYG (page 3, lines 21-29). However, it does not appear that the specification, including the claims, as originally filed, provides written support for fluorescent proteins derived from another fluorescent protein comprising a chromophore

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having three amino acid residues selected from the group consisting of SYG, SHG, TYG and THG in which any one or more amino acids is substituted for another.

In addition, claims 23-25 and 32 are directed to a genus of fluorescent proteins that specifically includes fluorescent proteins derived from GFP that comprise a chromophore having the amino acid sequence of THG.

Although the specification, including the claims, as originally filed, provides written support for the members of the claimed genus that comprise chromophores having the amino acid sequences of SYG, TYG and TYG, it does not appear to provide adequate written support for those comprising a chromophore having the amino acid sequence of THG. At page 3, lines 14-18, the specification discloses: "Surprisingly, we have found that a mutation, preferably a substitution, of the F amino acid residue at position 1 preceding the S of the SYG or SHG chromophore or the T of **the THG chromophore**, *in casu* position 64 in the predicted primary amino acid sequence, results in a substantial increase of fluorescence intensity apparently without shifting the excitation and emission wavelengths [emphasis added]." While this disclosure might be considered to provide written support for a chromophore having the amino acid sequence of THG, it is noted that the specification appears to include no other description of such a chromophore, or of a fluorescent protein, including a derivative of wild-type GFP, comprising such a chromophore. Moreover, it appears the specification fails to describe the production of members of the genus of fluorescent proteins derived from wild-type GFP that comprise such a chromophore, which have an amino acid at position 1 upstream from the chromophore that is different from the amino acid at the corresponding position in the wild-type GFP, such that the derivative exhibits an increased fluorescence intensity at temperatures of at least 30°C when expressed in a host cell. It is submitted that to be minimally supportive of the genus, it would be necessary that the specification adequately describe a variant of wild-type GFP that comprises the chromophore THG, rather than the wild-type chromophore SYG. Such a variant would necessarily be made upon the substitution of serine at "position 65" with threonine and the substitution of tyrosine at "position 66" with histidine. While the specification describes the production of variants of wild-type GFP by substituting serine

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at "position 65" with threonine or tyrosine at "position 66" with histidine, it does not describe the production of a variant by making both these substitutions.

These issues might be resolved if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support.

18. Claims 1-6, 8, 9, 23-25, 32, and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <<http://www.gpoaccess.gov/>>.

The claims are drawn to a genus of fluorescent proteins that are derived from "Green Fluorescent Protein (GFP)" or any "functional analogue" thereof, wherein the amino acid in position 1 preceding the "chromophore" has been mutated to provide "an increase in fluorescence intensity".

In considering the breadth of the claims, it is noted that the term "Green Fluorescent Protein (GFP)" is not expressly defined in the specification. In the absence of explicit definitions of its terms, the claims are given the broadest, reasonable interpretation that is consistent with the supporting disclosure and which would be understood by the artisan of skill in the relevant art.

The BioTech Life Sciences Dictionary, which is available on the Internet at <http://biotech.icmb.utexas.edu/search/dict-search.html>, defines the term "green fluorescent protein" as "[a] protein found in jellyfish which fluoresces, or glows green

visible light when excited by UV [ultraviolet] light with a wavelength of 395 nanometers" (Copyright © 1995-1998 The Trustees of Indiana University). However, at page 7, lines 11-13, for example, the specification discloses an embodiment of the invention is the "blue variant Y66H-GFP", which the specification teaches fluoresces, or glows blue visible light when excited. Accordingly, the claims are not limited to a fluorescent protein that fluoresces, or glows green visible light when excited by UV light with a wavelength of 395 nanometers. Moreover, the claims are not limited to a fluorescent protein that is a derivative of another fluorescent protein that has "an increased fluorescent intensity" at any particular emission band (i.e., the wavelength or range or wavelengths at the protein fluoresces) or relative to that of the fluorescent protein from which it was derived, since the derivative may emit light at a wavelength or range of wavelengths that differs from that at which the protein from which it was derived fluoresces.

At page 7, lines 23 and 24, the specification discloses that the claimed fluorescent protein may be derived from other fluorescent proteins, such as the fluorescent protein of the sea pansy *Renilla reniformis*. However, claim 4 recites the claimed fluorescent protein is derived from *Aequorea victoria* or *Renilla reniformis*; and as such, it would be understood that the claimed fluorescent protein is not necessarily a fluorescent protein derived from any particular fluorescent protein by mutation of the chromophore, such as a derivative of fluorescent protein of *A. victoria* or *R. reniformis*, but a fluorescent protein derived (i.e., isolated) from any source, including but not necessarily limited to *A. victoria* or *R. reniformis*. As such the claims are broadly, but reasonably interpreted to be directed to any fluorescent protein that is a naturally occurring homologue of the fluorescent proteins of either *A. victoria* or *R. reniformis*.

While the specification describes the amino acid sequence of "a preferred sequence of the gene encoding GFP derived from *A. victoria* (Figure 2; SEQ ID NO: 15), which putatively encodes the predicted amino acid sequence set forth as SEQ ID NO: 16, it fails to adequately describe any other member of the family of structurally and functionally related proteins to which the claims are directed.

As evidenced by Labas et al. (*Proc. Natl. Acad. Sci. USA.* 2002 Apr 2; **99** (7): 4256-4261), the family of “GFP”-like proteins is very diverse; and only recently has many of the recognized members of the family been isolated; see entire document (e.g., the abstract). Therefore, as further evidenced by Labas et al., the claims are directed to fluorescent proteins that are “derived” from members of a family of proteins that exhibit strikingly diverse features (abstract). For example, Labas et al. teaches that there are examples of fluorescent proteins emitting light of the same color, yet have different chromophores (paragraph bridging pages 4257 and 4258). As another example, Remington et al. (*Biochemistry.* 2005; **44**: 202-212) describes a naturally occurring yellow-fluorescent member of the GFP-like family of proteins having a novel three-ring chromophore; see entire document (e.g., the abstract). Remington et al. further describes variants of this protein produced by substituting other amino acids for lysine in the chromophore, which are green or red emitters (abstract). Remington et al. discloses that the remarkable diversity of coral reef coloration is in large part due to the presence its functionally diverse fluorescence proteins, which are homologs of the GFP of *A. Victoria*, having cyan, green, yellow, and red emissions, and of more distantly related non-fluorescent chromoproteins (page 202, column 1).

Again, the specification discloses that the claimed fluorescent protein may be derived from other fluorescent proteins, such as the fluorescent protein of the sea pansy *Renilla reniformis*. However, the specification merely describes the amino acid sequence of a preferred sequence of the gene encoding GFP derived from *A. victoria* without describing the amino acid sequence of the fluorescent homologue produced by *R. reniformis*. According to a disclosure that is available on the Internet at <http://www.biochemtech.uni-halle.de/PPS2/projects/jonda/index.htm>, as of November 1996, the amino acid sequence of the “GFP” of *Renilla* had not been determined (see “Introduction”, attached hereto, page 2 of 3) and a recent search of PubMed™ suggests that a complementary DNA (cDNA) molecule encoding the protein yet to be isolated.

It further considering the breadth of the claims, it is also noted that the term “functional analogue” is not defined in the specification. Given the plain ordinary meaning of the term “analogue”, then, the claims are drawn to a fluorescent protein that

derived from a protein that is structurally similar to a member of the genus of "green fluorescent proteins". The analogue, although structurally similar to a member of the GFP-like family of proteins, is not necessarily a fluorescent protein, since notably Labas et al. (*supra*) teaches that many members of the family were not identified until it was realized that such proteins are present in nonbioluminescent representatives of the class Anthozoa (page 4256, column 1). Matz et al. (*BioEssays*. 2002; **24**: 953-959) teaches that despite enormous interest in the possible specific features that any homologous proteins might possess, up to 1999, GFP of *A. victoria* remained the only known example (entire document, but particularly page 953, column 2). Matz et al. explains that the cause for delay in identifying homologs was caused largely by the fact that GFP of *A. victoria* is functionally inconspicuous, as there is no coloration or fluorescence visible to the naked human eye and the presence of the protein in jelly fish is only revealed during a flash of bioluminescence produced by the mechanical stimulation of the jelly fish (page 953, column 2).

In final consideration of the breadth of the claims, it is noted that the term "chromophore" is not defined in the specification. The term "chromophore" is generally used to describe the part of a visibly colored molecule responsible for light absorption over a range of wavelengths, thus giving rise to the color. As noted above, Labas et al. (*supra*), for example, teaches that members of the family of GFP-like proteins comprise structurally and functionally distinct chromophores. Therefore, just as the claims are not limited to fluorescent proteins derived from the fluorescent protein of *A. victoria*, the claims are not limited to fluorescent proteins derived from a fluorescent protein or functional analogue thereof comprising the chromophore of the fluorescent protein of *A. victoria*.

Given the facts that many members of the GFP-like family of proteins have only recently been isolated, that the members of the family of proteins are structurally and functionally disparate, that the parts of many of such proteins (e.g., amino acid residues) upon which the color of the protein depends (i.e., the chromophores) has yet to be described, and that the amino acid sequence of the fluorescent protein of *Renilla* was not determined as of the filing date sought by Applicant in this instance, it is

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submitted that the supporting disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See Noelle v. Lederman, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). In this instance, the specification merely describes a preferred sequence of the gene encoding GFP isolated from *A. Victoria* without particularly describing nucleic acids encoding other members of the GFP-like family of proteins (e.g., functional homologues of the GFP isolated from *A. Victoria*); moreover, it merely describes the particular effects upon the fluorescence of variants of this single example of a fluorescent protein produced by substituting tyrosine for histidine at the second position of its chromophore or by substituting serine for threonine at the first position, and then further substituting the phenylalanine preceding the chromophore for leucine, isoleucine, valine, alanine, glycine, or another amino acid, provided the resulting variant fluoresces with increased intensity relative to the exemplary protein. However, as explained above, the claims encompass fluorescent proteins derived from a genus of structurally and functionally disparate molecules and therefore the claimed fluorescent proteins vary both structurally and functionally; and as explained more fully in the scope of enablement rejection set forth below, even given benefit of the supporting disclosure, the skilled artisan cannot predict the consequence of other substitutions in the exemplary sequence, or these substitutions and others in the sequences of other GFP-like proteins from which the claimed fluorescent proteins are derived. Accordingly, the particular descriptions of the few examples of fluorescent proteins derived from the exemplary amino acid sequence of the GFP of *A. victoria* are not deemed adequate to describe the claimed genus as a whole. Absent the adequate description of a representative number of members of the genus of agents to which the claims are directed, the supporting

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disclosure amounts to no more than a mere invitation to identify other fluorescent proteins that fulfill the limitations of the claims.

Recognizing that the claims are directed (but not necessarily limited) to a variant of a fluorescent protein that has increased fluorescent intensity, relative to that of the fluorescent protein from which it was derived, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity does not provide an adequate written description of the genus. See *The Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. See *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). Moreover, “generalized language may not suffice if it does not convey the detailed identity of an invention.” *Id.* at 1892.

Furthermore, there is no language having the necessary degree of particularity that adequately describes the members of the claimed genus of fluorescent proteins that are derived from sources including but not limited to *A. victoria* or *R. reniformis*, or which are derived from the fluorescent proteins of either *A. victoria* or *R. reniformis*. A description of what a material does (i.e., it fluoresces with an increased intensity), rather than of what it is, does not suffice to describe the claimed invention.

Although the skilled artisan could potentially identify fluorescent proteins that have an increased fluorescent intensity relative to some other fluorescent protein by, for example, functionally screening cDNA libraries produced using nucleic acids isolated

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from organisms that bioluminesce, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In addition, as addressed above in the "new matter" rejection, claims 23-25 and 32 are directed to a genus of fluorescent proteins that are derived from "wild-type Green Fluorescent Protein (GFP) comprising a chromophore having three amino acid residues selected from the group consisting of SYG, SHG, TYG and THG". The specification describes the amino acid sequence of "a preferred sequence of the gene encoding GFP derived from *Aequorea victoria*" (page 7, lines 13 and 14; Figure 2; SEQ ID NO: 15), which putatively encodes the predicted amino acid sequence of "a wild-type Green Fluorescent Protein (GFP)" (i.e., SEQ ID NO: 16). As further disclosed at page 3, lines 10-12, this "wild-type GFP" comprises the chromophore SYG at positions 65-67 in the predicted primary amino acid sequence. However, it does not appear that the specification particularly describes a "wild-type GFP" comprising chromophores of SHG, TYG, or THG. In fact, the specification discloses that the blue fluorescing variant designated Y66H-GFP, which comprises the chromophore SHG, is not a "wild-type GFP" (i.e., natural GFP) but a recombinant fluorescent protein produced by random *in vitro* mutagenesis of a complementary DNA (cDNA) molecule encoding the naturally occurring protein (page 1, lines 19-28).

Furthermore, claim 24 is directed to a fluorescent protein according to claim 23, which further comprises an amino acid substitution involving one or more of the three

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amino acid residues of the chromophores SYG, SHG, TYG or THG. The specification provides describes substituting tyrosine in the middle position of the chromophore SYG with histidine (e.g., page 1, lines 19-28) and also describes substituting serine in the first position of the chromophore SYG with threonine (e.g., page 2, lines 10-13). It describes substitutions at the phenylalanine at the position preceding the first position of the chromophores SYG, SHG, and TYG (page 3, lines 21-29). However, it does particularly describe fluorescent proteins derived from another fluorescent protein comprising a chromophore having three amino acid residues selected from the group consisting of SYG, SHG, TYG and THG in which any one or more amino acids is substituted for another.

While it might be argued that the specification provides written support for the recitation of the claim language, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

See also: University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

As further addressed above in the “new matter” rejection, claims 23-25 and 32 are directed to a genus of fluorescent proteins that specifically includes fluorescent proteins derived from GFP that comprise a chromophore having the amino acid sequence of THG. At page 3, lines 14-18, the specification discloses: “Surprisingly, we have found that a mutation, preferably a substitution, of the F amino acid residue at position 1 preceding the S of the SYG or SHG chromophore or the T of the **THG chromophore**, *in casu* position 64 in the predicted primary amino acid sequence, results in a substantial increase of fluorescence intensity apparently without shifting the excitation and emission wavelengths-[emphasis added].” While this disclosure might be

considered to provide *in ipsis verbis* support for a chromophore having the amino acid sequence of THG, it is noted that the specification appears to include no other description of such a chromophore, or of a fluorescent protein, including a derivative of wild-type GFP, comprising such a chromophore. Moreover, it appears the specification fails to describe the production of members of the genus of fluorescent proteins derived from wild-type GFP that comprise such a chromophore, which have an amino acid at position 1 upstream from the chromophore that is different from the amino acid at the corresponding position in the wild-type GFP, such that the derivative exhibits an increased fluorescence intensity at temperatures of at least 30°C when expressed in a host cell. Therefore, regarding claims 23-25 and 32, it is submitted that to adequately describe a variant of wild-type GFP that comprises the chromophore THG, rather than the wild-type chromophore SYG, it would be necessary to describe the production and characterization of a variant made by substituting serine at "position 65" with threonine and tyrosine at "position 66" with histidine. While the specification describes the production of variants of wild-type GFP by substituting serine at "position 65" with threonine or tyrosine at "position 66" with histidine, it does not describe the production of a variant by making both these substitutions.

Finally, Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of fluorescent proteins, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to

practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

19. Claims 1-6, 8, 9, 23-25, 32, and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making** a fluorescent protein having an increased fluorescence intensity at the emission maxima, relative to the wild-type Green Fluorescent Protein (GFP) produced by *Aequorea victoria*, which comprises the amino acid sequence set forth in the instant application as SEQ ID NO: 16, by randomly mutagenizing amino acids 64-69 comprised within the naturally occurring chromophore of the wild-type GFP of *A. Victoria* and functionally screening resultant proteins to identify those having an increased fluorescence intensity at the emission maxima, relative to said wild-type GFP, **and more particularly for making** a fluorescent protein having the amino acid sequence set forth as SEQ ID NO: 22 and any other fluorescent proteins disclosed by the prior art, which are known to exhibit such spectroscopic properties, **does not reasonably provide enablement for making** a fluorescent protein derived from Green Fluorescent Protein (GFP) or any functional analogue thereof, wherein the amino acid in position 1 preceding the chromophore has been mutated to provide an increase in fluorescence intensity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As explained in the "written description" rejection, the claims are broadly but reasonably interpreted as encompassing a genus of fluorescent proteins differing from a member of a genus of functionally and structurally disparate homologs or variants of the green fluorescent protein (GFP) of *Aequorea Victoria*, including fluorescent proteins produced by different organisms, including, for example, *Renilla reniformis*.

The specification teaches different fluorescent proteins comprising the amino acid sequences set forth as SEQ ID NOs: 16, 18, 20, and 22.

The specification teaches the fluorescent protein comprising the amino acid sequence set forth as SEQ ID NO: 22 ("F64L-S65T-GFP") fluoresced with greater intensity at a temperature of 22°C following excitation at 470 nm than the fluorescent proteins of SEQ ID NO: 16 ("GFP") or SEQ ID NO: 20 ("F64L-GFP") (page 17, lines 26-28). However, the specification also teaches that the fluorescent protein of SEQ ID NO: 22 fluoresced with decreased intensity, relative to the fluorescent proteins of SEQ ID NO: 16 or SEQ ID NO: 20, at this temperature following excitation at 398 nm (page 17, lines 20-22). Accordingly, while the fluorescent protein of SEQ ID NO: 22 is capable of fluorescing with greater intensity than the fluorescent protein of SEQ ID NO: 16, it is only capable of doing so after excitation at a particular wavelength. At a temperature of 37°C and following excitation at this wavelength (i.e., 470 nm), the specification teaches the fluorescent proteins of SEQ ID NO: 20 or SEQ ID NO: 22 fluoresced longer (although not necessarily with increased intensity) following excitation than the fluorescent protein of SEQ ID NO: 16 (page 17, lines 29-31). Notably, since after 16 hours at 37°C, the fluorescent protein of SEQ ID NO: 16 ceased to fluoresce, it is not possible to assess the difference in the fluorescence intensity between that protein and the others that continued to fluoresce.

Furthermore, there is an assertion that the fluorescent protein of SEQ ID NO: 22, when expressed in cells incubated at 37°C prior to the measurement, fluoresces with increased intensity, relative to the fluorescent proteins of SEQ ID NO: 16 or SEQ ID NO: 20, when expressed in cells incubated in the same manner (page 19, lines 14-22). The specification refers to "Table 1", which presumably tabulates the data collected in the experiment described; however, as noted above in the objection to the specification, the table appears to have been omitted.

The prior art (e.g., Delagrange et al. (*Bio/Technology (NY)*. 1995 Feb; **13** (2): 151-154)) teaches fluorescent proteins having an increased fluorescence intensity at the emission maxima, relative to the wild-type Green Fluorescent Protein (GFP) produced

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by *Aequorea victoria*, which comprises the amino acid sequence set forth in the instant application as SEQ ID NO: 16, by randomly mutagenizing amino acids 64-69 comprised within the naturally occurring chromophore of the wild-type GFP of *A. Victoria* and functionally screening resultant proteins to identify those having an increased fluorescence intensity at the emission maxima, relative to said wild-type GFP.

Even given that already known in the art, the amount of guidance, direction, and exemplification disclosed by in the specification would not be sufficient to enable the skilled artisan to make the claimed invention without a need to perform an undue amount of additional experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

As further explained in the "written description" rejection, the amino acid sequence of the GFP of *Renilla reniformis* is not described in the specification; moreover, a cDNA encoding has not yet been isolated or described. Accordingly, the amount of guidance, direction, and exemplification disclosed in the instant application would not be sufficient to enable the skilled artisan to make the claimed invention without undue experimentation, since it would be necessary to first isolate a cDNA molecule encoding the GFP of *Renilla* before it would become practical to make the claimed fluorescent proteins, which are derivatives of the naturally occurring protein.

As also explained in the "written description" rejection, as evidenced by Labas et al. (*supra*) and Matz et al. (*supra*), it has only been recently discovered that homologs of the GFP of *A. Victoria* are produced by nonbioluminescent organisms, which before had

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hampered the successful isolation of nucleic acid molecule encoding these functional analogues and their characterization. Even so, since the specification does not teach the amino acid sequences of such analogues, it would first be necessary to isolate nucleic acid molecules encoding these homologs of the GFP of *A. victoria* before it would be possible to make the proteins or derivatives thereof having increased fluorescence intensity, as compared to some referenced fluorescent protein (e.g., the GFP of *A. Victoria*). However, in order to identify those that have an amino acid immediately preceding the chromophore that differs from that present at the corresponding position in the referenced fluorescent protein, or in order to deliberately mutagenize such fluorescent proteins to produce variants thereof, in accordance with the claims, it would also be necessary to identify the amino acids of which their chromophores are comprised. As evidenced by Labas et al. (*supra*) and Remington et al (*supra*), members of the family of GFP-like proteins include structurally and functionally distinct proteins having, in particular different chromophores and emitting light at different wavelengths, or not at all. Without knowledge of the amino acids of which their chromophores are comprised, it would not be possible to determine the identity of the amino acid preceding the chromophore.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed in the specification is not deemed sufficient to enable the skilled artisan to make the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

21. Claims 1-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Delagrange et al. (*Bio/Technology* (NY). 1995 Feb; 13 (2): 151-154).

Delagrange et al. teaches a fluorescent protein derived from the green fluorescent protein (GFP) of *Aequorea victoria* (wild-type GFP) by randomly mutagenizing the complementary DNA (cDNA) molecule encoding wild-type GFP; see entire document. Delagrange et al. discloses that the variants of wild-type GFP that were produced differ from wild-type GFP by amino acid substitutions at the position of the first amino acid preceding the cyclic tripeptide sequence, serine-dehydrotyrosine-glycine (SYG) of the chromophore, which occurs at positions 65-67 of the amino acid sequence of the wild-type protein (e.g., page 151, column 1; and page 152, Table 1). In particular, Delagrange et al. teaches a variant that was produced by substituting the naturally occurring phenylalanine at position 64 with leucine or glycine (e.g., page 152, Table 1). Furthermore, Delagrange et al. teaches that some of the variants differ from wild-type by substitutions at position 65; for example, in one variant, the serine at this position within the chromophore is replaced by glycine (e.g., page 152, Table 1).

While Delagrange et al. does not expressly teach that the chromophore of the wild-type GFP was mutated to provide an increase in fluorescence intensity, the objective sought in mutating wild-type GFP to produce the disclosed variants does not distinguish those variants from the claimed fluorescent proteins, since the objective sought in doing so does not materially, structurally, or functionally alter the proteins produced by the process. Nevertheless, "[a]s a practical demonstration the spectral

separability" of the wild-type protein and the variants produced, Delagrange et al. teaches that one of the variants (i.e., RSGFP4) has increased fluorescence intensity, relative to wild-type GFP, at 505 nm, since the emission maxima of the wild-type protein is 510 nm (e.g., paragraph bridging pages 152 and 153; page 153, Figure 3; and page 151, column 1). Accordingly, because Delagrange et al. asserts that all of the variants have distinct spectral properties, absent a showing of any difference, the variants produced by substituting the naturally occurring phenylalanine at position 64 with leucine or glycine are deemed the same as the claimed invention.

Delagrange et al. does not expressly teach that when expressed in cells incubated at a temperature above 30°C, the variants have increased fluorescence intensity, relative to wild-type GFP. However, Delagrange et al. expressed the variants in cells incubated at 37°C before isolating the protein from the cells and determining that the cells expressing the variants produced protein having increased fluorescence, relative to protein isolated from cells expressing wild-type GFP, which were incubated under the same conditions (e.g., page 154, column 2). Therefore, although Delagrange et al. does not expressly teach that when expressed in cells incubated at a temperature above 30°C, the variants have increased fluorescence intensity, relative to wild-type GFP, because the variants produced by cells incubated at 37°C exhibited increased fluorescence, relative to wild-type GFP, the variants are deemed the same as the claimed invention.

The Office, however, does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed protein. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed protein is different than those taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

22. Claims 23-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Delagrange et al. (*Bio/Technology* (NY). 1995 Feb; 13 (2): 151-154).

As explained above, claims 23-25 are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure. For this reason, the claims do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed. Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely July 19, 2000.

Delagrange et al. teaches that which is set forth in the above rejection of claims 1-5 under 35 U.S.C. 102(a). As explained in the rejection above, absent a showing of any difference, the fluorescent proteins disclosed by Delagrange et al. is deemed the same as the claimed invention.

The Office, however, does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed protein. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed protein is different than those taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

23. Claims 23-25 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,804,387 A.

As explained above, claims 23-25 and 32 are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure. For this reason, the claims do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed. Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely July 19, 2000.

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U.S. Patent No. 5,804,387 A ('387) teaches a fluorescent protein derived from the green fluorescent protein (GFP) of *Aequorea victoria* (wild-type GFP) by substituting the phenylalanine preceding the naturally occurring chromophore SYG with leucine and the serine at the first position of the naturally occurring chromophore with tyrosine; see entire document (e.g., the abstract; columns 7 and 8, Table 3). '387 discloses that this variant of the GFP of *A. Victoria*, which is designated "GFPmut1", has a fluorescence intensity that is an order of magnitude higher than that of wild-type GFP excited at 488 nm after expression in *E. coli* (e.g., abstract). Furthermore, '387 discloses the higher fluorescent intensity of the variant was observed at high temperatures (e.g., 37°C) (e.g., column 3, lines 33-42). '387 teaches the variant is useful as a tool for marking a protein or cell of interest by covalently conjugating the variant to the protein of interest or by recombinantly producing a fusion protein comprising the variant and the protein of interest (e.g., column 1, lines 20-35; and column 10, lines 49, through column 11, line 45).

Therefore, absent a showing otherwise, the fluorescent protein, or fusion compound thereof, disclosed by the prior art is deemed the same as the claimed fluorescent protein or fusion compound thereof.

Double Patenting

Statutory

24. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in

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scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

25. Claims 7 and 40 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 15 of prior U.S. Patent No. 6,172,188 B1. This is a double patenting rejection.

Claim 15 of the prior patent is drawn to a polypeptide comprising the amino acid sequence of SEQ ID NO: 20, which is a "green fluorescent protein". SEQ ID NO: 20, as set forth in the specification of the prior patent, is identical to SEQ ID NO: 22, as set forth in the instant application. Claims 7 and 40 of the instant application are drawn to a fluorescent protein having the amino acid sequence of SEQ ID NO: 22, which the specification defines as a "green fluorescent protein". Accordingly, the scope of instant claims 7 and 40 and prior claim 15 are not different.

26. Claims 7 and 40 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 10 of copending Application No. 10/947,178. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim 10 of the copending application is drawn to a polypeptide comprising the amino acid sequence of SEQ ID NO: 20, which is a green fluorescent protein (GFP). SEQ ID NO: 20, as set forth in the copending application, is identical to SEQ ID NO: 22, as set forth in the instant application. Claims 7 and 40 of the instant application are drawn to a fluorescent protein having the amino acid sequence of SEQ ID NO: 22, which the specification defines as a "green" fluorescent protein. Accordingly, the scope of instant claims 7 and 40 and copending claim 10 are not different.

Non-Statutory

27. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

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and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

28. Claims 1-6, 23-25, and 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 15 of U.S. Patent No. 6,172,188 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 1-6, 23-25, and 41 are drawn to a genus of fluorescent proteins. Claims 1-7 of the prior patent are also drawn to a genus of fluorescent proteins, whereas claim 15 is drawn to a member of said genus of fluorescent proteins. The fluorescent proteins encompassed by prior claims 1-7 and 15 anticipate the broader genus of fluorescent proteins to which claims 11-6, 23-25, and 41 of the instant application are drawn.

29. Claims 1-6, 23-25, and 41 are directed to an invention not patentably distinct from claims 1-7 and 15 of commonly assigned U.S. Patent No. 6,172,188 B1. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth above in the obviousness-type double patenting rejection.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP

§ 2302). Commonly assigned U.S. Patent No. 6,172,188 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

30. Claims 1-6, 8, 23-25, 32, and 41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 10, and 11 of copending Application No. 10/947,178. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 1-6, 8, 23-25, 32, and 41 are drawn to a genus of fluorescent proteins or fusion compounds, which comprise such fluorescent proteins. Claims 1, 2, and 11 of the copending application are drawn to a genus of fluorescent proteins, whereas claim 10 is drawn to a member of said genus of fluorescent proteins. The fluorescent proteins encompassed by copending claims 1, 2, 10, and 11 anticipate the broader genus of fluorescent proteins to which claims 1-6, 8, 23-25, 32, and 41 of the instant application are drawn.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

31. Claims 1-6, 8, 9, 23-25, 32, and 41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/296,953. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 1-6, 8, 9, 23-25, 32, and 41 are drawn to a genus of fluorescent proteins or fusion compounds, which comprise such fluorescent proteins linked to polypeptide, or more particularly, a kinase. Claims 1-8, 11, and 12 of the copending application are drawn to a genus of fluorescent proteins, whereas claims 9 and 10 are drawn to a member of said genus of fluorescent proteins. The fluorescent proteins or fusion compounds encompassed by copending claims 1-12 anticipate the broader genus of fluorescent proteins or fusion compounds to which claims 1-6, 8, 9, 23-25, 32, and 41 of the instant application are drawn.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

32. Claims 1-6, 8, 9, 23-25, 32, and 41 are directed to an invention not patentably distinct from claims 1-12 of commonly assigned copending Application No. 10/296,953. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth above in the obviousness-type double patenting rejection.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/296,953, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting

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inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

33. No claim is allowed.

34. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Cormack et al. (*Gene*. 1996; **173**: 33-38) teaches a fluorescent protein derived by mutagenesis from GFP isolated from *A. victoria*. U.S. Patent No. 6,090,919 A teaches a fluorescent protein derived from the green fluorescent protein (GFP) of *A. victoria* (wild-type GFP) by substituting the phenylalanine preceding the naturally occurring chromophore SYG with leucine and the serine at the first position of the naturally occurring chromophore with tyrosine.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLR
Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
May 18, 2005